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Diffusion Tensor Imaging Analysis of Frontal Lobes in Pediatric Traumatic Brain Injury

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Abstract

This study examined the use of diffusion tensor imaging in detecting white matter changes in the frontal lobes following pediatric traumatic brain injury. A total of 46 children (ages 8-16 years) with moderate to severe traumatic brain injury and 47 children with orthopedic injury underwent 1.5 Tesla magnetic resonance imaging (MRI) at 3 months postinjury. Conventional MRI studies were obtained along with diffusion tensor imaging. Diffusion tensor imaging metrics, including fractional anisotropy, apparent diffusion coefficient, and radial diffusivity, were compared between the groups. Significant group differences were identified, implicating frontal white matter alterations in the injury group that were predictive of later Glasgow Outcome Scale ratings; however, focal lesions were not related to the Glasgow Outcome Scale ratings. Injury severity was also significantly associated with diffusion tensor imaging metrics. Diffusion tensor imaging holds great promise as an index of white matter integrity in traumatic brain injury and as a potential biomarker reflective of outcome.

Keywords

frontal lobe, traumatic brain injury, diffusion tensor imaging, outcome, Glasgow Coma Scale, Glasgow Outcome Scale

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Traumatic brain injury is a leading cause of death and disability in children, creating significant medical, social, and financial burdens on healthcare, social service, family, and educational systems.[1-3] A major objective of contemporary traumatic brain injury research is to improve methods of detecting the neuropathology of traumatic brain injury. Such advancements may improve the ability to predict outcomes and lessen the multifaceted burdens associated with traumatic brain injury. Over 3 decades of traumatic brain injury research have shown that improved computed tomography and magnetic resonance imaging (MRI) techniques have greatly enhanced the ability to better specify trauma-related abnormalities in the brain following traumatic brain injury.[4] However, although computed tomography and MRI represent routine diagnostic tools in both the acute as well as chronic assessment of traumatic brain injury, the use of conventional MRI sequences have not been especially predictive of outcome.[5] A limitation of conventional computed tomography and/or MRI is that while these procedures are sensitive in detecting trauma-related abnormalities, focal abnormalities associated with traumatic brain injury have not been robustly predictive of outcome.[6] This is likely because of the diffuse pattern of injury in traumatic brain injury, especially at the moderate to severe level of injury. As a result, there is disruption of white matter integrity caused by traumatic axonal injury, an event that encompasses diffuse axonal injury.[7,8] Thus, without a marker of white matter integrity to identify tissue damage, conventional imaging only

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provides a portion of the necessary clinical information to make accurate predictions of traumatic brain injury outcome. Trauma-induced white matter damage from traumatic axonal injury/diffuse axonal injury also disrupts the connectivity of the brain. Therefore, simply knowing the location of a lesion or specific trauma-related abnormality does not necessarily provide information on how that lesion disrupts connectivity with other brain regions or neural networks. Diffusion tensor imaging, a relatively new MRI technique, reveals considerable biological information about white matter integrity with implications for improved detection of white matter health and functionality in a variety of disorders, including traumatic brain injury.[9-14]

Several studies have now been published showing the utility of diffusion tensor imaging metrics in defining the pathological effects of traumatic brain injury on white matter integrity and predicting outcome.[15-32] The majority of these studies were completed in adults. Therefore, the determination of whether diffusion tensor imaging provides better prediction over conventional lesion identification and localization in children is not well understood. To that end, if diffusion tensor imaging findings in pediatric traumatic brain injury advance the diagnostic armamentarium and provide improved prognostication, such results can lead to improved treatment and outcome, thereby lessening the social and medical burdens of traumatic brain injury.

The physics of diffusion tensor imaging incorporate special pulsed magnetic field gradients into a standard MRI sequence, allowing for increased sensitivity to the diffusion of water molecules.[12,33] In normal brain tissue there are physical boundaries that restrict the diffusion of water in white matter, favoring movement of water parallel to axons and deterring movement perpendicular to axons. This restriction of diffusion is referred to as fractional anisotropy and is the ratio of anisotropy to isotropy. Fractional anisotropy ranges from 0 to 1 where values near 0 are representative of isotropy or random diffusion (eg, as a result of injury). Conversely, values close to 1 are representative of water diffusion parallel to organized axonal structures in normal tissue. Previous studies have shown that fractional anisotropy is sensitive to pathological changes such as demyelination, axonal damage, and other microstructural white matter changes. Additionally, 2 other common quantitative diffusion tensor imaging measures are typically obtained, including the apparent diffusion coefficient, which denotes the speed of water diffusion in all directions, and radial diffusivity, which denotes direction and speed of diffusion perpendicular to the axon. Cellular membrane breakdown or processes such as demyelination can increase extracellular space, thereby increasing apparent diffusion coefficient. Diffusion tensor imaging is also quite sensitive in tracking normal development of white matter (eg, myelination) in the child's brain, making it a particularly useful imaging tool in detecting neuropathological changes that occur in the pediatric population.[14]

As previously mentioned, conventional computed tomography and MRI findings have limited predictive ability in defining recovery from traumatic brain injury. It is anticipated that diffusion tensor imaging, because of its greater sensitivity in assessing white matter pathology and development, will prove to be a better predictor of pediatric traumatic brain injury outcomes than conventional imaging. Although diffusion tensor imaging provides a variety of metrics that can assess white matter integrity within any brain region in the child with traumatic brain injury, the challenge remains to determine which region of interest would be most predictive of outcome. Neuropathology and brain imaging studies have consistently shown a craniocaudal gradient of lesions whereby prefrontal gray and white matter are the most frequent areas damaged, although temporal lobe damage is a close second.[34] The frontal lobe is also the largest of the 4 lobes and its relationship to the bony anterior cranial fossa makes it particularly vulnerable to injury, deformation, and cortical contusion—all of which likely disrupt the integrity of white matter pathways traversing the frontal lobes.[34] Furthermore, because the frontal lobes are the location of neural networks supporting executive function, emotion, and memory, which collectively form a common domain of neurobehavioral sequelae associated with traumatic brain injury,[35] we selected the frontal lobe as our region of interest. We explored the relation between diffusion tensor imaging findings in this region and outcome in pediatric traumatic brain injury, while including children with orthopedic injury as controls. Diffusion tensor imaging studies in adults and children provide support for examining frontal lobe diffusion tensor imaging following traumatic brain injury in relation to outcome.[29,36] Unlike adults, in pediatric traumatic brain injury there are not only injury effects, but a consequent disruption of the normal white matter maturation of the frontal lobes as well. As a result, we hypothesized that frontal lobe diffusion tensor imaging changes in pediatric traumatic brain injury would relate to injury severity and outcome based on the Glasgow Coma Scale[37] and the Glasgow Outcome Scale,[38] respectively, more than structural damage within the frontal lobes as identified by conventional MRI.

Methods

Participants

Analysis of diffusion tensor imaging at 3 months postinjury was performed on a cohort of 46 children with moderate to severe traumatic brain injury (32 male, 14 female) who were admitted to children's hospitals in Houston, Dallas, and Miami. This included Children's Medical Center Dallas (Dallas, Texas), Parkland Memorial Hospital (Dallas, Texas), Cook Children's Medical Center (Fort Worth, Texas), Baylor Institute for Rehabilitation (Dallas, Texas), Our Children's House at Baylor (Dallas, Texas), Texas Children's Hospital (Houston, Texas), Jackson Memorial Hospital (Miami, Florida), and Miami Children's Hospital (Miami, Florida). The subjects were prospectively enrolled as part of a larger longitudinal study of pediatric traumatic brain injury. All participants in the traumatic brain injury group had a primary diagnosis of moderate to severe closed head injury, as designated by a Glasgow Coma Scale score of 3 to 12, and, if a Glasgow Coma Scale was 13 to 15, participants had computed tomography evidence of intracranial abnormality. Children in the

Table 1. Demographic and Injury Characteristics of the Samples

	Traumatic Brain Injury (n = 46)	Orthopedic Injury (n = 47)
Age at injury (years)[a]	M = 13.62, SD = 2.83, range = 7.10-17.21	M = 12.03, SD = 2.49, range = 7.05-16.56
Time postinjury (months)	M = 4.19, SD = 1.23, range = 1.94-7.70	M = 4.15, SD = 0.93, range = 2.70-7.11
Gender	32 male, 14 female	35 male, 12 female
Race/ethnicity	5 AA, 1 AI, 0 A, 1 Bi, 19 C, 20 H	13 AA, 0 AI, 1 A, 2 Bi, 15 C, 16 H
Handedness	45 right, 1 left	40 right, 7 left
Maternal education (years)	M = 12.63, SD = 2.90, range = 5.00-18.00	M = 13.68, SD = 2.78, range = 7.00-20.00
Socioeconomic composite index	M = −0.01, SD = 0.81, range = −1.86-1.43	M = 0.13, SD = 0.86, range = −1.52-1.89
Mechanism of injury[a]	25 MVA, 4 RV/ATV, 2 bike, 9 fall, 1 sports, 4 hit by vehicle, 1 other	7 MVA, 1 RV/ATV, 3 bike, 9 fall, 1 hit by falling object, 22 sports, 2 hit by vehicle, 2 other
Glasgow Coma Scale	M = 7.39, SD = 4.31, range = 3-15	N/A
Glasgow Outcome Scale	43.2% good recovery, 36.4% moderate disability, 20.4% severe disability	N/A

Abbreviations: M, mean; SD, standard deviation; AA, African American; AI, American Indian; A, Asian; Bi, Biracial; C, Caucasian; H, Hispanic; MVA, motor vehicle accident; N/A, not applicable; RV, recreational vehicle; ATV, all terrain vehicle.

[a] Significant group difference. Since age significantly differed between the groups, it was included in all models. Mechanism of injury differed, as expected, with significantly more children in the traumatic brain injury group being injured as a result of high-velocity mechanisms such as motor vehicle accidents and more orthopedic injury children injured as a result of sports/play activities.

traumatic brain injury group had a score less than 4 on an Abbreviated Injury Scale[39] for areas of the body other than the head and absence of postresuscitation hypoxia or hypotension exceeding 30 minutes in duration. A comparison group of 47 children with extracranial orthopedic injuries was also scanned at approximately 3 months postinjury. Use of these children as a control group was intended to control for risk factors predisposing children to injury, and to equate for nonspecific factors resulting from hospitalization. Children in the orthopedic injury group were admitted to the hospital, but had an Abbreviated Injury Scale score under 5 and no intracranial abnormality on head computed tomography, if one was performed. Approximately 63% of children and adolescents in the traumatic brain injury group were injured as a result of high-speed mechanisms including motor vehicle, motorcycle, or recreation vehicle accidents as opposed to approximately 17% of children in the orthopedic injury group who were injured by similar mechanisms (see Table 1 for additional demographic and injury information). All participants (both groups) were English-speaking and had no premorbid neurological or major psychiatric diagnosis (eg, autism, psychotic disorder, bipolar disorder, pervasive developmental disorder). No child in either group had a history of child abuse, previous hospitalization for head injury, prematurity (<37 weeks gestation), or low birth weight (<2500 g). All participants were screened for metal and other contraindications before undergoing MRI. Participants with traumatic brain injury or orthopedic injury provided informed consent through a process approved by the institutional review boards of the participating centers including the imaging portions pertaining to this study.

MRI Acquisition

As part of the study design, MRI, outcome, and cognitive assessments were planned for 3 months postinjury to allow degenerative changes to stabilize on neuroimaging.[40,41] All participants underwent MRI without sedation on Philips 1.5 Tesla Intera scanners (Philips, Cleveland, OH) at Texas Children's Hospital-Houston, the Rogers MRI Center, University of Texas Southwestern Medical Center, Dallas, or the Miami Children's Hospital in Miami, using comparable platforms and software. Regular quality assurance testing was performed on all 3 scanners including American College of Radiology phantom and Weisskoff testing for echo planar imaging sequences, and all scanners were consistently noted to be within an acceptable range throughout the study.

A coronal T2-weighted fluid-attenuated inversion recovery sequence was used (1100 msec TR, 140 msec TE, 5.0-mm slices) for estimation of lesion size and location. For this sequence, a 220-mm field of view was used with a reconstructed voxel size of 0.86 × 0.86 × 5.0 mm. For diffusion tensor imaging acquisition, transverse multislice spin echo, single shot, echo planar imaging sequences were used (10 150.5 ms repetition time, 90 ms echo time, 2.7-mm slices, 0-mm gap). A 256-mm field of view was used with a measured voxel size of 2.69 × 2.69 × 2.7 mm and a reconstructed voxel size of 2.00 × 2.00 × 2.7 mm. Diffusion was measured along 15 directions (number of b value = 2, low b value = 0, and high b value = 860 s/mm^2). To improve signal to noise ratio, high b images were acquired twice and were averaged. Each acquisition took approximately 5 minutes 45 seconds, and 55 slices were acquired.

Lesion Analysis

Areas of signal abnormality were identified and traced by a board certified neuroradiologist (JH) using fluid-attenuated inversion recovery imaging previously described.[13] Forty-two of the 46 children with traumatic brain injury had frontal lesions apparent on fluid-attenuated inversion recovery imaging; lesion volumes ranged from 0 to 46.04 mm^3 (mean = 8.10 ± 12.61 mm^3). Thirty-eight of 46 participants with traumatic brain injury also had extrafrontal lesions. No trauma-related lesions were identified in the orthopedic injury group.

Diffusion Tensor Imaging Pre- and Postprocessing

The Philips diffusion affine registration tool was used to remove shear and eddy current distortion and head motion prior to calculating fractional anisotropy maps with Philips fiber-tracking 4.1V3 beta 4 software.[42] Regions of interest were drawn manually using the protocols described below, and then the automated Philips 3 dimensional fiber-tracking tool was utilized to determine fiber tracks passing through regions of interest. Mean fractional anisotropy, radial diffusivity, and apparent diffusion coefficient of the fiber system,

which was automatically generated by the software, were used as the quantitative measures for diffusion tensor imaging variables. The algorithm for fiber tracking is based on the fiber assignment by continuous tracking method.[33] For each of the regions of interest listed below, we used standard parameters where tracking terminated if the fractional anisotropy in the voxels decreased below 0.2 or if the angle between adjacent voxels along the track was larger than 6.75 degrees. The rationale for examining the frontal lobes was its known vulnerability in traumatic brain injury and its importance in frontal mediated cognitive function.

Frontal Protocol

Measures of frontal white matter were obtained from both hemispheres. Regions of interest were drawn in the coronal plane on a slice just anterior to the first slice where the genu of the corpus callosum was visible. Right and left sides were calculated separately and all white matter within the boundaries was included.

Reliability

Reliability was assessed via diffusion tensor imaging tractography of the frontal lobe of 6 orthopedic injury and 6 traumatic brain injury participants by 2 trained raters. Statistical analysis was conducted using SPSS 15.0 for Windows (SPSS Inc, Chicago, IL), in which intraclass correlation coefficients were all above 0.90 for fractional anisotropy, apparent diffusion coefficient, and radial diffusivity measures. Subsequent interreliability by a single rater of all subjects in this study also achieved an intraclass correlation coefficient above 0.90 for these same diffusion tensor imaging metric values.

Glasgow Coma Scale

Glasgow Coma Scale[37] scores, ranging from 3 to 15, assessed eye, verbal, and motor response following injury. The clinical scale was performed by trauma physicians in the emergency department who had no prior knowledge of imaging results.

Glasgow Outcome Scale

The Glasgow Outcome Scale of Jennett and Bond[38] was adapted for use with children based on the criteria described by Wilde and colleagues[13] and was obtained concurrently with MRI. The scale consists of the following ratings: (1) good recovery, (2) moderate disability, (3) severe disability, (4) persistent vegetative state, and (5) death. In this sample, 43.2% of the children with traumatic brain injury achieved good recovery, 36.4% had moderate disability, and 20.4% had severe disability. Glasgow Outcome Scale ratings were assessed by a neuropsychology technician at 3 months postinjury without prior knowledge of imaging results.

Statistical Analysis

Independent sample t tests were used to examine group differences in maternal education, socioeconomic status as measured by the socioeconomic composite index,[43] age of injury, and time postinjury. Fisher's exact test was used to examine group differences in gender and lateral dominance. A general linear model analysis approach (repeated measures analysis of covariance) was used to examine group differences in mean fractional anisotropy, apparent diffusion coefficient, and radial diffusivity in the frontal hemispheres bilaterally, with group and hemisphere as variables and age as a covariate. Critical assumptions of the general linear model (including the heterogeneity of slopes of the covariates) were examined and no violations were noted. Paired t tests were used to examine right versus left hemisphere differences in fractional anisotropy, radial diffusivity, and apparent diffusion coefficient within each group. Spearman's rho correlations were used to examine the relation between mean fractional anisotropy, radial diffusivity, and apparent diffusion coefficient and lesion volume in the frontal lobes within the traumatic brain injury group maintaining an alpha of $P < .05$ for a priori analyses. Additionally, Spearman's rho correlations were used to examine the relation between diffusion tensor imaging indices and Glasgow Coma Scale score. Finally, we utilized a multinomial logistic regression model to examine whether mean fractional anisotropy, apparent diffusion coefficient, and radial diffusivity could predict outcome as measured by the Glasgow Outcome Scale score.

Results

Group Characteristics

The t tests revealed no significant difference for the socioeconomic composite index, maternal education, or time postinjury. Fisher's exact test revealed no significant group differences in handedness, race/ethnicity, or gender. The t tests revealed a significant difference in age at injury ($t[91] = -2.87$, $P = .005$) in that the traumatic brain injury group was older; therefore, age was controlled for in all subsequent analysis.

Group Differences in Diffusion Tensor Imaging between Orthopedic Injury and Traumatic Brain Injury Groups

General linear model analysis revealed significantly higher fractional anisotropy, lower apparent diffusion coefficient, and lower radial diffusivity values in the orthopedic injury group compared to the traumatic brain injury group in the frontal lobes. Table 2 details results of group difference analyses. In within-group analyses, fractional anisotropy, apparent diffusion coefficient, and radial diffusivity did not differ significantly between right and left hemispheres.

Relationship between Diffusion Tensor Imaging, Glasgow Coma Scale, and Glasgow Outcome Scale

Diffusion tensor imaging indices were significantly related to the Glasgow Coma Scale score in the traumatic brain injury group (r coefficients ranging from .359 to .447 and P values ranging from .002 to .017), with lower fractional anisotropy and higher diffusivity relating to greater injury severity (lower Glasgow Coma Scale score) as detailed in Table 3. Radial diffusivity proved to have a stronger correlation with respect to the Glasgow Coma Scale than other diffusion tensor imaging metrics such as fractional anisotropy and apparent diffusion coefficient in the frontal lobe ($r = 0.444$ with left and .447 with right, P values = .003 and .002, respectively).

Significant correlations were demonstrated between diffusion tensor imaging indices and the Glasgow Outcome Scale in the traumatic brain injury group in the right hemisphere (fractional anisotropy: $r = -.412$, $P = .005$; apparent diffusion coefficient:

Table 2. Group Differences in Frontal Lobes

	Mean Indices		Statistics	
Frontal Regions	OI (SD)	TBI (SD)	*T* value	*P* value
Right FA	0.38 (0.02)	0.35 (0.03)	5.65	<.0001
Right ADC	0.82 (0.04)	0.88 (0.12)	−2.81	<.0068
Right RD	0.64 (0.04)	0.70 (0.11)	−3.58	.0007
Left FA	0.38 (0.02)	0.35 (0.03)	6.18	<.0001
Left ADC	0.83 (0.04)	0.87 (0.07)	−3.37	.0012
Left RD	0.64 (0.04)	0.69 (0.07)	−4.46	<.0001

Abbreviations: FA, fractional anisotropy; ADC, apparent diffusion coefficient; RD, radial diffusivity; OI, orthopedic injury; TBI, traumatic brain injury; SD, standard deviation.

Table 3. Relation between Diffusion Tensor Imaging and the Glasgow Coma Scale, and the Glasgow Outcome Scale within the Traumatic Brain Injury Group

	Glasgow Coma Scale			Glasgow Outcome Scale		
Region	Mean FA *r* (*P* value)[a]	Mean ADC *r* (*P* value)[a]	Mean RD *r* (*P* value)[a]	Mean FA *r* (*P* value)[a]	Mean ADC *r* (*P* value)[a]	Mean RD *r* (*P* value)[a]
Right frontal	.403 (.007)[b]	−.388 (.009)[b]	−.447 (.002)[b]	−.412 (.005)[b]	.335 (.036)[b]	.380 (.011)[b]
Left frontal	.359 (.017)	−.387 (.009)[b]	−.444 (.003)[b]	−.429 (.004)[b]	.208 (.176)	.275 (.071)

Abbreviations: FA, fractional anisotropy; ADC, mean diffusion; RD, radial diffusivity.
[b] Spearman's rho correlation coefficient between diffusion tensor imaging measure and Glasgow Coma Scale, Glasgow Outcome Scale.
[a] Significant correlation ($P < .05$).

$r = .335, P = .036$; radial diffusivity: $r = .380, P = .011$) such that higher fractional anisotropy, and lower radial diffusivity and apparent diffusion coefficient, were associated with better recovery (Table 3). A significant negative correlation was also observed for the relation between mean fractional anisotropy of the left ($r = -.429$, $P = .004$) frontal lobe and the Glasgow Outcome Scale score. The right frontal apparent diffusion coefficient ($r = -.388, P = .026$) and radial diffusivity ($r = -.447, P = .011$) also correlated significantly with the Glasgow Outcome Scale score. The left frontal lobe radial diffusivity ($r = .275$, $P = .071$) was marginally correlated with the Glasgow Outcome Scale score. There was no significant correlation between mean apparent diffusion coefficient in the left frontal lobe and the Glasgow Outcome Scale score. Multinomial logistic regression analysis indicated an increasing probability of achieving good recovery with increased fractional anisotropy in the right ($\chi^2[1] = 6.75$, $P = .009$) and the left (χ^2 [1] = 8.16, $P = .004$) hemispheres. Multinomial logistic regression analysis revealed no significant relation between the Glasgow Outcome Scale outcome and apparent diffusion coefficient. Multinomial logistic regression analysis revealed marginal significance for radial diffusivity in the right (χ^2 [1] = 3.51, $P = .061$) but not left hemisphere.

Lesion Size

There was no significant correlation between diffusion tensor imaging indices fractional anisotropy, radial diffusivity, and apparent diffusion coefficient and frontal lesion volume. Further logistic regression analyses with lesion size and the diffusion tensor imaging metrics reflected no significant contribution of lesion size to the Glasgow Outcome Scale or to the relation of diffusion tensor imaging metrics to the Glasgow Outcome Scale.

Discussion

This study demonstrated strong group differences in terms of frontal lobe diffusion tensor imaging metrics between participants with moderate to severe traumatic brain injury compared to an orthopedic injury group. As expected, comparisons of the groups at 3 months postinjury demonstrated reduced frontal lobe fractional anisotropy, increased radial diffusivity, and increased apparent diffusion coefficient in the traumatic brain injury group, reflective of white matter damage. More importantly, these diffusion tensor imaging changes are related to the Glasgow Coma Scale severity of injury and the Glasgow Outcome Scale outcomes at 3 months postinjury.

Consistent with our finding that frontal lobe diffusion tensor imaging indices of fractional anisotropy, apparent diffusion coefficient, and radial diffusivity were sensitive to injury severity indexed by a lower Glasgow Coma Scale, previous diffusion tensor imaging studies of frontal lobes in adult traumatic brain injury have shown a similar pattern.[36] In our study, the strongest correlation with the Glasgow Coma Scale scores was found with radial diffusivity. Changes in radial diffusivity can be particularly

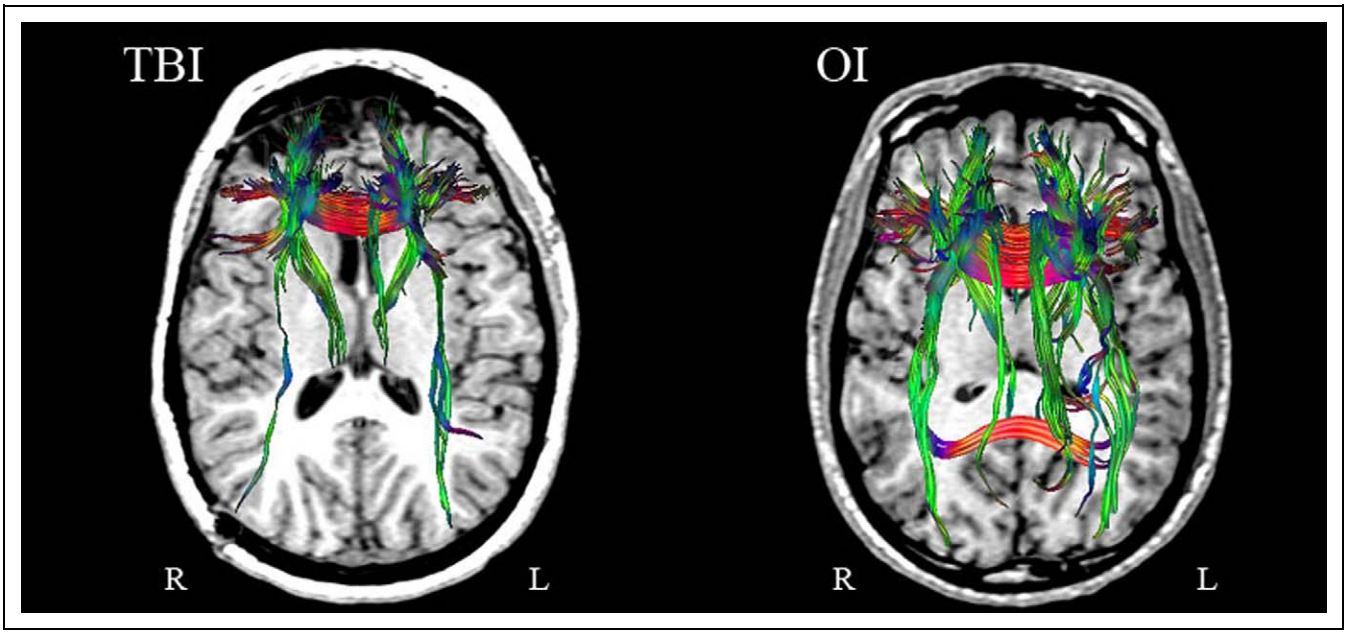

Figure 1. Diffusion tensor imaging tractography overlaid on a T1-weighted axial image (left) from a 12-year-old girl who had sustained a severe traumatic brain injury after falling from the back of a truck moving at a low speed (initial Glasgow Coma Scale score = 7), striking the back of her head, and sustaining frontal contusions. Tractography and T1-weighted MRI from an age- and sex-matched child with orthopedic injury at approximately the same level are on the right. There is extensive frontal encephalomalacia in the child with traumatic brain injury at 3 months postinjury, but the real significance of the frontal damage is seen when tractography maps are created by seeding identical areas in the coronal plane, at a level just anterior to the genu of the corpus callosum in both children. The normal tracts from the frontal region at this level course posteriorly via central white matter pathways as well as the cingulum. Extensive interhemispheric projection across the anterior corpus callosum that includes an extensive network of integrated bifrontal pathways can be visualized in the child with orthopedic injury. All of these pathways are reduced and thinned in the child with traumatic brain injury. Note at this level, in the child with traumatic brain injury, there was also an absence of callosal fibers across the posterior corpus callosum.

sensitive in detecting myelin integrity.[44] Similar findings were noted by Ewing-Cobbs and colleagues[25] in the diffusion tensor imaging assessment of the corpus callosum in children. This study further supports the concept that radial diffusivity is a sensitive diffusion tensor imaging marker in determining the severity of injury and extent of neuronal damage following traumatic brain injury.

In the current study, there was a significant correlation between diffusion tensor imaging measures in the frontal lobe and the Glasgow Outcome Scale, with higher fractional anisotropy and lower radial diffusivity correlating with good recovery. A strong relation was found between indices of white matter integrity based on fractional anisotropy and the probability of good outcome. These findings are similar to those of previous studies examining other regions of interest, including the corpus callosum and select brain stem regions in pediatric traumatic brain injury.[28,32] Overall, we found that diffusion tensor imaging metrics of white matter frontal lobe integrity were related to the Glasgow Outcome Scale, suggesting that diffusion tensor imaging holds promise as a potential biomarker that can be useful in guiding treatment and predicting outcome in pediatric traumatic brain injury.

Focal Frontal Lesions Versus Diffusion Tensor Imaging

As expected, the majority of patients evidenced frontal lesions. In fact, only 4 of the 46 participants with brain injury did not show evidence of such pathology on conventional MRI. Interestingly, there was no significant relationship between the volume of frontal lesions and diffusion tensor imaging indices in the traumatic brain injury group, suggesting that pathology seen on MRI is not a specific indicator of white matter microstructural pathology.

As discussed above, while all but 4 of the traumatic brain injury participants had documented frontal lesions, the presence of these lesions was not predictive of an outcome based on the Glasgow Outcome Scale. This raises the question of why there is such a poor relationship between the documented focal pathology of the frontal lobe and the outcome. Figure 1 provides a potential explanation, where another feature of diffusion tensor imaging is used to show white matter abnormalities. The technique of white matter tractography demonstrates how disruptive a focal, frontal pole lesion can be in changing white matter projecting fiber tracks within the frontal lobes. As can be seen in this child with frontal damage, there is considerable focal frontal encephalomalacia from old frontal pole contusions. There is some ventricular asymmetry, but not dramatic ipsilateral to the most prominent encephalomalacia. There is also a notable white matter signal difference that can be visually appreciated in the conventional anatomical image (see Figure 1). However, when identical areas are seeded in what appears to be intact frontal white matter, dramatically

different tractography arises showing marked thinning of anterior-posterior aggregate projecting pathways including cingulate projections. As a result, the low fractional anisotropy and sparse white matter tracts as shown in Figure 1 implicate reduced connectivity of the brain following injury, whereas the focal pathology reflects only 1 dimension of the lesion, but not necessarily the loss of connectivity.

Strengths, Limitations, and Future Studies

Few studies have specifically examined the role of diffusion tensor imaging in the frontal lobes in pediatric traumatic brain injury, particularly in a large multicenter prospective longitudinal study of this nature. Nonetheless, given the number of potential brain regions that could be examined, including a more refined analyses of the frontal regions may enhance our findings. Moreover, with a larger sample size, more regions could be reliably examined to make a comparative analysis of diffusion tensor imaging regions of interest, which were not completed in this investigation. For example, the study by Niogi et al[16] took a novel approach to examining neuropsychological correlates of neuroimaging findings in traumatic brain injury. This group examined specific tracts in the brain in terms of specific cognitive functions and outcome, such as memory and attention related to the uncinate fasciculus. In the current investigation, fractional anisotropy was assessed in a single slice that likely captured major frontal pathways, but certainly not all, and no specific tracts were targeted. It may very well be the case that better outcome prediction will come from more specific diffusion tensor imaging determinations within more defined regions of interest, tracts, or neural systems. For example, emotional sequelae are well known to compound rehabilitation outcomes following traumatic brain injury, and it may be that examining diffusion tensor imaging characteristics within limbic white matter connections will yield more important findings in terms of neurobehavioral outcome.

Studies have shown that increased morbidity and long-term disability are associated with a greater severity of brain injury in children.[45-48] This sample of children was examined at approximately 3 months postinjury. We do not know how predictive these findings are of the outcome as time progresses, particularly when one takes into account the influence of psychosocial variables.[49] As a result, more diffusion tensor imaging studies are needed to assess moderate to severe traumatic brain injury in children to strengthen the associations noted in this study. A particular emphasis must be placed on the frontal lobe region given its primary role in cognitive tasks and its vulnerability for injury.

Conclusion

This investigation represents the first prospective diffusion tensor imaging study to analyze frontal lobe regions in moderate to severe pediatric traumatic brain injury, with particular assessment of group differences and outcomes. Diffusion tensor imaging indices differed significantly between the traumatic brain injury and orthopedic injury groups, and also correlated with the Glasgow Coma Scale and the Glasgow Outcome Scale, highlighting the utility of diffusion tensor imaging as a prognostic and diagnostic tool. As a future research and clinical metric, diffusion tensor imaging has the potential to monitor improvements in neural functioning during recovery as well as assess the effects of pharmacological and behavioral therapy.

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Declaration of Conflicting Interests

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